

Implications of FDARA 2017 on Pediatric Cancer Drug Development

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FDA Advisory Committee Consensus Statement

- **Pediatric** oncology drug development should generally be **coordinated** with oncology drug development for **adults**, as part of an **overall drug development plan**

Challenges and Opportunities in Pediatric Oncology Drug Development

Opportunities

- Scientific Discovery
 - Molecular drivers/validated targets
 - Available targeted therapies/immunotherapies ?
- Infrastructure
 - Clinical trial networks
 - Investigator/Patient/Family Engagement
 - Advocacy organizations
- Technology/Big Data/“Real world”
- **Evolving drug development paradigm**
- Emerging biomarkers
 - CTCs, ctDNA, MRD

Challenges

- Low Incidence
- Heterogeneity
 - Disease
 - Developmental
 - Genomic signatures
- Formulation requirements
- **Preclinical model/testing limitations**
- **Limited extrapolation opportunities**
- Financial
- Combination drug development needed

• **Leveraging Adult Discovery**

Approaches to Pediatric Oncology Drug Development

- Use of current approaches continue but innovation and streamlining required
- New approaches needed: Evolving Drug Development Paradigm
 - increasing knowledge of genomic basis and heterogeneity of pediatric cancers
 - emergence of targeted therapies demonstrating large treatment effects in small subsets – “**Precision Medicine**”
significant delay in the pediatric setting
 - compressed drug development timelines in adults with innovative designs: Seamless trial designs(Phase1/2, expansion cohorts)

Targeted Therapy Opportunities in Pediatrics

- Crizotinib – ALCL and ?NBL
- Brentuximab – HL and ALCL
- BCR – ABL TKIs in CML and Ph+/-like HR ALL
- Ruxolitinib in CRLF2+/JAK2 + ALL
- Selumetinib in PNF and LGA
- Dabrafenib in HGG, LGG, and melanoma (BRAF V600E+)
- Inotuzumab and Blinotumomab in ALL



Leveraging Adult Discovery and Development: The Legislation



Pediatric Research Equity Act (PREA)

- Authorizes FDA to **require** pediatric assessments
- Triggered by NDA/BLA submission or a supplement with a new indication, new active ingredient, dosage form, dose regimen or route of administration
- **Applies only to indication(s) included in the submission**
- **Drugs with Orphan Designation are exempted from PREA**
- FDA can grant full or partial waiver or deferral for pediatric studies if specific criteria are met
- **No relevance to Pediatric Cancer**

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079756.pdf>

Best Pharmaceuticals for Children Act (BPCA)

- Provides a financial incentive to companies to **voluntarily** conduct pediatric studies under a Pediatric Written Request (WR)
- A sponsor may request the FDA to issue a WR by submission of a Proposed Pediatric Study Request (PPSR) or FDA may issue WR without PPSR
- PPSR should contain rationale for studies, detailed study designs and plans for formulation development

PREA and BPCA Programs

PREA

- Drugs and biologics
- Mandatory** studies
- Requires studies **only in indication(s) under review**
- Orphan indications exempt** from studies
- Pediatric studies must be labeled

BPCA

- Drugs and biologics
- Voluntary** studies
- Studies relate to entire moiety and **may expand indications**
- Studies may be requested for orphan indications
- Pediatric studies must be labeled

BPCA: Written Request (WR)

- **Considerations when reviewing a PPSR for a potential WR**
 - What is the public health benefit?
 - Are the study designs feasible; sufficient to support dosing, safety and efficacy?
 - Have all populations and conditions been addressed?
 - Are there other products already approved for the condition?
 - **WRs can be issued EARLY**
 - **WRs can be amended:** Emerging results may impact pediatric development plan

Selecting candidate therapies for WRs

- **Mechanism of action** suggests potential for activity
- Scientific rationale exists for the drug to be evaluated in pediatric cancers
- Activity in preclinical models of pediatric cancers
- Efficacy has been shown in a related adult cancer
- Evidence that the therapy will have similar efficacy and reduced toxicity compared to existing therapy
- Has potential to improve a clinical outcome for the pediatric patient

Shortening the timeline for development of drugs for pediatric cancers

- More efficient dose-finding studies (rolling six; continuous reassessment model) , modeling and allometric scaling
- Adult RP2D when no adult MTD
- Expanding FIP study sites- improved patient access and study enrollment
- Innovative trial designs/ development strategies
 - Histology-agnostic development
 - Adaptive design – with disease cohorts
 - Master protocols
 - Embedding pediatric trials in adult studies
- Including pediatric cohort on select FIH trials
- Enrolling adolescents (children) on relevant disease-specific trials

Promoting expedited development of new drugs for pediatric cancers

- BPCA Pediatric Oncology Working Group holds quarterly meetings with representatives of the academic community to discuss **promising new agents for pediatric evaluation** through the WR mechanism
- Office of Pediatric Therapeutics coordinates a monthly Pediatric Cluster meeting with international regulators (EMA, HC, TGA, PMDA) for information exchange and discussion of specific product development, safety concerns and general scientific issues to assure alignment of pediatric development plans: PSPs, WRs and PIPs

Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)



- Forum where industry sponsors can obtain input from key academic and community opinion leaders regarding an ongoing or potential pediatric development program
 - gauge investigator interest in exploring pediatric development programs for products in various stages of adult development
 - select possible drug candidates for a Written Request
 - provide feedback to industry on trial design, pediatric regulations
 - Interactive discussion of a key topic in designing trials for pediatric patients with cancer
- Ideal to come early in drug development timeline even prior to NDA submissions
- Sponsors are encouraged to seek an invitation if there are questions regarding or interest in a pediatric development program.
- Encourage and facilitate remote participation by EMA
- Provide opportunity for international investigator input



Expanding the Authority of PREA

- Indication-based trigger to MOA-based
- Requiring pediatric studies based on known molecular mechanism of action could significantly increase the number of pediatric studies under PREA
- Proposed PREA amendment to require that certain drugs (including biologic agents) developed for adult cancer indications be evaluated for a pediatric cancer indication when there is evidence that the drug affects specific molecular targets and/or molecular mechanisms that are common to both adult and pediatric tumors

RACE for Children Act:

- Incorporated as Title V of the FDA Reauthorization Act (FDARA), enacted August 18, 2017
- **Requires** evaluation of new molecularly targeted drugs and biologics “intended for the treatment of adult cancers and directed at a **molecular target substantially relevant to the growth or progression of a pediatric cancer.**”
- **Molecularly targeted pediatric cancer investigation:** clinically meaningful study data, “using appropriate formulations, regarding dosing, safety and preliminary efficacy to inform potential pediatric labeling.” [FDARA Title V Sec 504 (a)(3)(A) or FD&C Act Sec. 505B (a)(3)(A)].
- Elimination of **orphan exemption from pediatric studies** for cancer drugs directed at relevant molecular targets.

Implications

- Establish with NCI, update regularly, and post on FDA website a list of “relevant” targets (1 year)
- Establish and post a list of non-relevant targets leading to waivers for pediatric studies (1 year)
- Work with NCI, Pediatric Subcommittee of ODAC, PeRC, investigators, sponsors, experts, and advocates
- Convene an open public meeting to refine/generate lists (1 year)
- Issue guidance on implementation (2 years)

Status

- Multi-stakeholder workshop (February 20, 2018): Developing a framework for target selection/designation: Friends of Cancer Research
- Target classification and criteria for determining relevance, process for updating lists, and additional considerations for decision-making for pediatric evaluation
- Open Public meeting: 1)April 20, 2018 at FDA- Review molecular target lists. 2) Pediatric subcommittee of ODAC, June 18/19, 2018- review/comment on lists and considerations; process for prioritizing same in class agents- working with external constituents
- Planning and implementation coordinated with internal FDA programs- Office of Pediatric Therapeutics, Division of Pediatrics and Maternal Health, Office of Regulatory Policy, and Office of Chief Counsel
- Advising sponsors of new conditions and requirements for iPSPs for **new** applications with planned submission dates after 8/18/2020

Molecular Target

A molecule in human cells that is **intrinsicly associated** with a particular disease process such as etiology, progression, and/or drug resistance. To be referred to as a target, there must be evidence that by addressing the target with a small molecule, biologic product, or other treatment intervention, a desired therapeutic effect is produced resulting in the alteration of the disease process.

Strategies for Identification

- Gene sequencing
- Expression profiling
- CMA
- Focused proteomics
- Pathway/phenotypic analysis
- Functional screening(siRNA, shRNA, CRISPR)
- *In vitro* or *in vivo* validation

Target Classification

- Resulting from specific gene abnormalities; present in a critical biologically related pathway or exhibit a synthetic, lethal relationship to a gene abnormality
- Intrinsic to cancer cell lineage or developmental stage
- Contributing to functional aspects of tumor micro-environment (stroma, infiltrating immune cells)
- Essential elements of cancer (and normal) cells

Factors Related to Relevance

- Identification of the target in a pediatric cancer (gene defect, intrinsic or differential expression by cancer cell)
- Target function relevant to etiology or resistance
- Effect of target modulation; in vivo, in vitro, synergy in biologic/rational combination
- Clinical experience; adult and pediatric
- Existence of predictive biomarkers
- Cell surface access of immune-directed targets



Considerations for Application of Target List to Product Development for Children

- Biologic plausibility
- Evidence of serious, deleterious (lethal) effects on critical developmental processes
- Toxicity profile
- Benefit: Risk analysis
- Formulation issues
- Pre-clinical studies and access to product
- Global pediatric development plans
 - International collaboration-clinical trials and coordination of regulatory requirements

Successful Implementation

- Transparent process
- Recognize/anticipate emerging scientific discovery
- International collaboration in designation and prioritization
- Recognize/address anticipated, potentially adverse consequences
- Global coordination/collaboration